

The University of Chicago

STUDIES ON SYNTHETIC DRUGS

I. PARTIAL REDUCTION OF SOME ALKYL
QUATERNARY SALTS OF PYRIDINE
AND QUINOLINE CARBONAMIDES

II. STUDIES TOWARD THE SYNTHESIS OF
4-METHYL-5, 5-DIALKYLURACIL

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1938

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TSU SHENG MA

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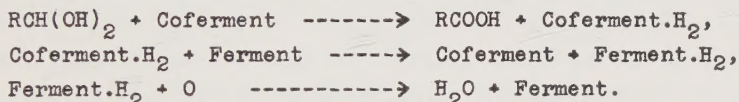
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I. PARTIAL REDUCTION OF SOME ALKYL QUATERNARY SALTS OF PYRIDINE AND QUINOLINE CARBONAMIDES

The chemistry of pyridine carboxylic acid amide has recently attracted the attention of the biochemist since the discovery that nicotinic acid amide is an important constituent of cozymase from yeast¹ and of coferment from horse blood cells,² and that the same compound is also a very potent curvative agent for pellagra.³ It has been definitely established that the reactivity of cozymase and coferment is due to their reversible oxidation-reduction property, and that the group responsible for this property is the nicotinic acid amide group in the co-enzymes. It is postulated that the co-enzymes act as hydrogen transporting agent through the absorption of two atoms of hydrogen from a donor and their subsequent removal by the ferment:



This theory is supported by the fact that the co-enzyme takes up two atoms of hydrogen per molecule when reduced with sodium hydro-sulfite, and that the product is oxidized reversibly by means of potassium ferricyanide. On the other hand, if the co-enzyme is more vigorously reduced, for instance, by catalytic hydrogenation in presence of platinum, six hydrogen atoms are taken up and the product cannot be oxidized reversibly. The same phenomenon is exhibited by quaternary salts of nicotinic acid amide. Identical changes in absorption spectra are also shown by the co-enzyme and the quaternary pyridinium salts during the oxidation-reduction process. These findings have led P. Karrer and co-workers to undertake an extensive study on dihydropyridine derivatives in

¹v. Euler, Alber and Schlenk, Z. physiol. Chem., **240**, 113 (1936).

²Warburg and Christian, Biochem. Z., **285**, 156 (1936).

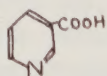
³Elvehjem, Madden, Strong and Wooley, J. Am. Chem. Soc., **59**, 1767 (1937).

order to elucidate the structure of the co-enzymes.¹

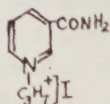
Some preliminary investigations in this laboratory have indicated that tetrahydropyridine and quinoline derivatives are potent oxytocic agents. It was therefore desirable to investigate and evolve methods for the preparation of these classes of substances. No simple methods are at present available for the synthesis of the partly reduced pyridine and quinoline derivatives.

The first attempt was to prepare the alkyl iodide derivatives of some pyridine and quinoline carbonamides and reduce them with sodium hydrosulfite. It was expected that these compounds and their partial reduction products might possess useful physiological activities, particularly the stimulating effect on smooth muscles. Three acids were chosen for the present investigation, namely, nicotinic acid, cinchoninic acid and quinaldinic acid. The reason for this choice was two-fold: First, this investigation would throw some light on the effect on the reactivity of the tertiary nitrogen due to the presence of an carbonamido group in the α -, β -, γ - positions. Secondly, since the quinoline ring is the basic skeleton of many plant alkaloids, the study of cinchoninic and quinaldinic acids might be of some interest in the field of pharmaceutical chemistry.

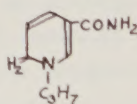
Nicotine was used as the starting material for nicotinic acid (I). The acid was transformed to the amide and the latter was treated with n-propyl iodide to give nicotinic acid amide n-propiodide (3-carbonamido-1-n-propylpyridinium iodide) (II). The quaternary salt thus obtained was reduced by sodium hydrosulfite in sodium carbonate solution under an atmosphere of nitrogen. N-n-propyl-o-dihydro-nicotinic acid amide (3-carbonamido-1-n-propyl-1,6-dihydropyridine) (III) was produced. It was crystal-



(I)



(II)



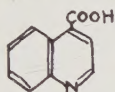
(III)

lized by using a large volume of ether and the pure product (rhombic tablets) melted at 96° . It is a powerful reducing agent.

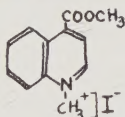
¹Karrer et al., *Biochem. Z.*, 285, 297 (1936); *Helv. Chim. Acta*, 19, 811, 1028 (1936); *Ibid.*, 20, 55, 72, 418, 622 (1937); *Ibid.*, 21, 223 (1938).

freely soluble in water. The aqueous solution of the compound was tested for oxytocic property but was found to be inactive. Attempts were made to reduce the N-n-propyl-o-dihydro-nicotinic acid amide to N-n-propyl-tetrahydro-nicotinic acid amide by controlled hydrogenation in presence of platinum oxide catalyst. A gummy solid was obtained which did not show any oxytocic effect.

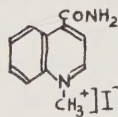
Cinchoninic acid amide methiodide (4-carbonamido-1-methyl-quinolinium iodide) (VI) was used as representative of γ -carboxylic acid amide alkyl iodide for the reduction experiment. The mother acid (IV) was made from cinchonine. For the preparation of the quaternary salt of the amide, one could condense the amide with alkyl iodide according to the regular procedure. However, for the preparation of the methiodide of cinchoninic acid amide, a simple method was developed. When cinchoninic acid was treated with dimethylsulfate and then potassium iodide, the methiodide of cinchoninic acid methyl ester (V) was produced. This compound was converted readily to the desired cinchoninic acid amide methiodide by boiling with concentrated ammonium hydroxide solution. When



(IV)



(V)

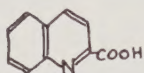


(VI)

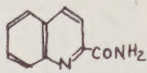
cinchoninic acid amide methiodide was treated with sodium hydro-sulfite in sodium carbonate solution, reduction took place. However, no definite reduction product was isolated. The soap-like solid which first separated showed reducing property, but this property disappeared on further treatment.

While nicotinic and cinchoninic acid amides form quaternary salts with alkyl iodides, quinaldinic acid amide (VIII) was found to be inert toward this group of reagents. Preliminary trials by heating quinaldinic acid amide with n-propyl iodide in a pressure bottle for 8 hours showed that the amide remained unchanged. Fortunately, quinaldinic acid amide was found to react with dimethylsulfate. By adding potassium iodide to the reaction product, quinaldinic acid amide methiodide (2-carbonamido-1-methyl-quinolinium iodide) (IX), a new compound, m. p. $209-210^{\circ}$, was obtained in form of yellowish green monoclinic plates. This compound was also formed by boiling methyl quinaldinate methiodide (X), prepared

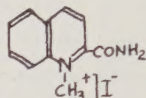
from methyl quinaldinate and dimethylsulfate, with concentrated ammonium hydroxide solution. It is of interest in this connection that quinaldinic acid, as contrasted with cinchoninic acid, is not attacked by dimethylsulfate.



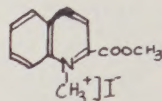
(VII)



(VIII)



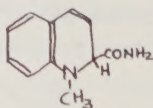
(IX)



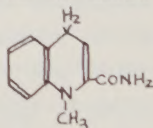
(X)

Two different methods of preparation of quinaldinic acid (VII) from quinaldine were studied. The first method involved the conversion of quinaldine to ω -oxymethyl-quinaldine followed by oxidation with nitric acid. The second method consisted of bromination to ω -tribromquinaldine followed by hydrolysis. The second method was found to be more suitable.

In the reduction of quinaldinic acid amide methiodide with sodium hydrosulfite in sodium carbonate solution, two different solid products were obtained. One solid (A) separated immediately after the reduction and was collected on a filter. After purification, it melted at $153-154^{\circ}$. A second solid (B) separated from the filtrate on standing over night. It turned purple and then black at 160° , gradually sintered at 180° , but did not melt until 225° . Both solids were strong reducing agents. Analysis showed absence of sulfur and halogen. The nitrogen contents appeared to indicate that both were impure N-methyl-dihydro-quinaldinic acid amide (XI and XII). Both of these materials showed



(XI)



(XII)

considerable oxytocic activity. Results obtained by method of Dale and Laidlaw¹ on guinea-pig uterus are shown in the graph on the following page.

While the investigation was in progress, the writer's at-

¹Burn, Methods of Biological Assay, Oxford University Press, 1928, p. 30.

tention was called to a communication of Karrer and co-workers¹ to the effect that they had failed to prepare the partial reduction products of isonicotinic and α -picolinic acid amides. They ascribed this difference from the ready reducibility of the quaternary salts of nictinic acid amides to the de-activating effect of the acid amide group in the α - and γ - positions with respect to the tertiary nitrogen. The findings of the present investigation, on the other hand, showed that in the quinoline series, the presence of carbonamido group in α - and γ - positions did not interfere with the reducibility of the quaternary quinolinium salts. Whereas the carbonamido group in α - position exerted decidedly blocking effect toward the formation of alkyl quaternary quinolinium salts, once the quaternary salt was prepared, it could be reduced by sodium hydrosulfite without difficulty.

¹Karrer, Kahnt, Epstein, Jaffé and Ishii, Helv. chim. Acta, 21, 232 (1938).

EXPERIMENTAL PART

I. Partial Reduction of Nicotinic Acid Amide n-Propiodide

Preparation of nicotinic acid, $\text{NC}_5\text{H}_4\text{.COOH}(3)$.--Nicotinic acid was prepared by oxidation of the crude 95% nicotine purchased from Tobacco By-product and Chemical Corporation, Louisville, Kentucky, according to the procedure described by McElvain.¹ The product melted at 228-229° (uncor.). The yield was 73% of theory.

Preparation of nicotinic acid amide, $\text{NC}_5\text{H}_4\text{.CONH}_2(3)$.--Attempts were made to prepare nicotinic acid amide directly from the acid by the action of thionyl chloride followed by ammonia. The result was not satisfactory. The amide was then prepared through the ethyl ester,² made by refluxing nicotinic acid (50 g.) with absolute ethanol (150 cc.) and concentrated sulfuric acid (100 g.). The ester was rectified under reduced pressure. It boiled at 123° under 35 mm. pressure. The yield of the ethyl ester was 67% of theory. The ethyl ester (15 g.) was mixed in a stoppered flask with ammonium hydroxide solution saturated with ammonia at -10° (10 cc.) and the mixture allowed to stand in the refrigerator for 5 days. Nicotinic amide separated out in form of white needles. The solid was collected on a filter. It melted at 127-128°. The filtrate on evaporation gave a second crop of less pure product. Yield: 89-96% of theory. Recrystallized from acetone, nicotinic acid amide was obtained as white needles, melting at 129-130°.

Preparation of nicotinic acid amide n-propiodide, $\text{C}_3\text{H}_7\text{I.NC}_5\text{H}_4\text{.CONH}_2(3)$.--Nicotinic acid amide (6 g.) and n-propyl iodide (152 g.) were heated in a pressure bottle at 125-130° for 5 hours. After removal of the excess n-propyl iodide, the residue was dissolved in 10 cc. of boiling water. The solution was filtered, and nicotinic acid amide n-propiodide was precipitated by the addition of 40 cc. of ethanol and 160 cc. of ether. The qua-

¹McElvain, Organic Syntheses, Vol. IV, p. 49 (1925).

²Camps, Archiv der Pharmazie, **240**, 353 (1902).

ternary salt, in form of light yellow hexagonal plates, was collected on a filter and dried at 100° . The yield was 83% of the-ory. It melted at $180-181^{\circ}$.

Reduction of nicotinic acid amide n-propiodide.--Nicotinic acid amide n-propiodide (1.2 g.) was dissolved in 25 cc. of water. A solution of sodium carbonate (4.5 g.) in 25 cc. of water was added. A current of nitrogen was passed through the flask over the solution. Sodium hydrosulfite (4.2 g.) was gradually introduced. Yellow or orange color appeared immediately and the solution turned turbid followed by the separation of oil drops in 25 minutes. After one hour, the oil was extracted six times with 30 cc. portions of ether. The ether extracts were combined and after drying over sodium sulfate, the solution was evaporated to dryness in a vacuum desiccator. Fine yellow plates were obtained. The solid melted at $84-86^{\circ}$ and weighed 0.38 g. (56% of the theoretical yield). The product was recrystallized from hot ether (300 cc.). Upon evaporation in a vacuum desiccator to about two-thirds of the original volume, crystals began to appear. The solution was concentrated to about 25 cc. and the crystals were collected on a filter. The product was in form of light yellow rhombohedral tablets, and melted at $96-97^{\circ}$. The melting point checked with that reported by Karrer and Stare¹ who assigned it to be N-n-propyl-o-dihydro-nicotinic acid amide, $C_3H_7.NC_5H_5.CONH_2$ (3). Examined under the polarizing microscope, the crystal showed high birefringence and high dispersion. It gave a bi-axial interference figure with a large optic angle.

The compound was readily soluble in chloroform and water. Its solution precipitated silver from silver nitrate solution, reduced potassium ferricyanide and decolorized methylene blue immediately in the cold. On standing in a stoppered tube, the crystals gradually changed from yellow to brownish red color and turned sticky. Its reducing power, however, was still very strong after standing for 9 months.

Several experiments were tried to reduce the dihydro-compound to the tetrahydro-compound by hydrogenation of the former in alcohol and in ether solutions using platinum oxide catalyst. After the calculated volume of hydrogen was absorbed, the solution gave only gummy solid on evaporation. The gummy solid and

¹Karrer and Stare, Helv. chim. Acta, 20, 421 (1937).

the pure N-n-propyl-o-dihydro-nicotinic-acid amide were tested for oxytotic property and were found to be inactive.

II. Partial Reduction of Cinchoninic Acid Amide Methiodide

Preparation of cinchoninic acid, $\text{NC}_9\text{H}_6\text{.COOH}$ (4).--The method of Deckner and Remfry¹ was used. Commercial cinchonine was oxidized by potassium dichromate in sulfuric acid solution. After removing the chromium by precipitation with ammonium hydroxide, cinchoninic acid was obtained by concentration of the filtrate and recrystallized from water. The yield varied with different batches of cinchonine. From 50 g. of the alkaloid, 9 to 17.5 g. of cinchoninic acid, melting at 248-249°, were obtained (31-59% of the theoretical yield).

Preparation of cinchoninic acid amide, $\text{NC}_9\text{H}_6\text{.CONH}_2$ (4).--Unlike the case of nicotinic acid, cinchoninic acid could be converted to the amide through the acid chloride by means of thionyl chloride. The acid chloride was not isolated and was treated directly with ammonia. Cinchoninic acid (5 g.) was refluxed with excess thionyl chloride (30 cc.) for 30 minutes. The unchanged thionyl chloride was distilled off. The solid residue was suspended in anhydrous benzene (50 cc.), and cooled in the ice-salt bath. A current of ammonia gas was passed through the suspension for 20 minutes, followed by the addition of 25 cc. of concentrated ammonium hydroxide. The solid was collected on a filter and recrystallized from acetone. Cinchoninic acid amide was obtained as white elongated tablets. It melted at 180-181°. The yield was 60%.

Formation of cinchoninic acid amide ethiodide, $\text{C}_2\text{H}_5\text{I.NC}_9\text{H}_6\text{.CONH}_2$ (4).--When cinchoninic acid amide (1.7 g.) was refluxed with ethyl iodide (33 g., 20 mole eq.) for 5 hours, no reaction took place. However, the quaternary salt was formed when the mixture was heated in a pressure bottle in an oil bath at 120° for 4 hours. After removal of the excess ethyl iodide, the solid was recrystallized from 75% ethanol. Cinchoninic acid amide ethiodide precipitated out as yellow rhombic plates, melting at 218-219°. The yield was 53% of theory.

Preparation of methyl cinchoninate methiodide,

¹Deckner and Remfry, J. prakt. Chem.(2), 79, 344 (1909).

$\text{CH}_3\text{I} \cdot \text{NC}_9\text{H}_8 \cdot \text{COOCH}_3(4)$.--Deckner and Remfry¹ observed that when cinchoninic acid was heated with dimethylsulfate, both the carboxyl group and the tertiary nitrogen were attacked, and that the methyl cinchoninate methiodide, obtained by precipitation with potassium iodide, was converted to cinchoninic acid amide methiodide by heating with concentrated ammonium hydroxide. This reaction was confirmed, and was found to be a convenient method for the preparation of cinchoninic acid methiodide without passing through the amide. Cinchoninic acid (14 g.) was mixed with dimethylsulfate (23 g.) and heated in an oil bath at 120° for 2 hours. The reaction mixture was then transferred to a beaker containing 40 cc. of boiling water. Pulverized potassium iodide (27 g.) was added. Crimson red colored precipitate in form of orthorhombic tablets came down on cooling and was collected on a filter. Recrystallized once from 95% ethanol, the product melted at $174-175^\circ$. The yield was 53% of theory. Pure methyl cinchoninate methiodide melted at 178° , but the product obtained was pure enough for the step following.

Conversion to cinchoninic acid amide methiodide,

$\text{CH}_3\text{I} \cdot \text{NC}_9\text{H}_8 \cdot \text{CONH}_2(4)$.--Methyl cinchoninate methiodide (10 g.) was refluxed with concentrated ammonium hydroxide solution (30 cc.) for 30 minutes. Upon cooling, the reaction mixture was acidified and potassium iodide (6 g.) was added. Orange colored precipitate came down on standing which was separated by filtration. The filtrate upon dilution with equal volume of ethanol and evaporation gave a second crop of the product. The yield was 54% of theory. Cinchoninic acid amide methiodide crystallized from 70% ethanol in form of orange yellow needles, melting at $234-235^\circ$.

Reduction of cinchoninic acid amide methiodide by sodium hydrosulfite.--Cinchoninic acid amide methiodide (1.4 g.) was dissolved in 25 cc. of water. The solution was filtered, and 4.5 g. of sodium carbonate dissolved in 25 cc. of water was added. The solution was placed in an atmosphere of nitrogen. Sodium hydrosulfite (4 g.) was introduced in portions. Differing from the reduction of nicotinic acid amide n-propylidide, the hydrosulfite did not dissolve very readily, but solution was effected by stirring and breaking up the white solid collected at the bottom of the flask with a glass rod. The solution turned turbid immedi-

¹Ibid., p. 347.

ately upon the addition of sodium hydrosulfite. Then brownish yellow soap-like precipitate separated out and floated on the surface. The precipitate dissolved readily in chloroform in which solvent the original cinchoninic acid amide methiodide was completely insoluble. After 30 minutes to one hour, the reaction mixture was extracted with seven 30 cc. portions of chloroform. The chloroform solution was brownish yellow. It reduced silver nitrate and potassium ferricyanide solutions in the heat. After drying over sodium sulfate, the chloroform extract was evaporated to dryness in a vacuum desiccator. About 0.2 g. of dark brown gummy solid was obtained. The gum was dissolved in 5 cc. of chloroform. It reduced silver nitrate only very slightly. The chloroform solution gave amorphous precipitate upon addition of ligroin or xylene, but the effort to obtain the product as crystalline solid was not successful.

In another experiment, the reaction mixture after reduction was extracted with ether instead of chloroform. The ether solution gave a very small amount of gummy residue on evaporation to dryness. The gum dissolved in chloroform and showed very slight reducing power.

III. Partial Reduction of Quinaldinic Acid Amide Methiodide

Preparation of quinaldinic acid, $C_9H_6N.COOH(2)$.--Quinaldinic acid was prepared from quinaldine by two different methods.

a. Method of Besthorn and Ibele¹.--Quinaldine (40 g.) was heated with 40% formaldehyde (70 g.) in a pressure bottle in the boiling water bath for 56 hours. The reaction mixture was steam distilled to remove the unchanged quinaldine. The residue was transferred to a 3-liter flask and oxidized with C. P. nitric acid (900 cc.) for 8 hours over the steam bath. Quinaldinic acid nitrate was obtained by concentration of the solution. It precipitated out as yellowish monoclinic prisms, melting at 199-200°. The nitrate was converted to ammonium quinaldinate by suspension in water (200 cc.), neutralization with concentrated ammonium hydroxide and evaporation of the solution. The residue was again dissolved in hot water (200 cc.) and the quinaldinic acid was

¹Vanino, "Präparativen Chemie," Steuttgart, 1923, Vol. II, p. 808.

precipitated as the lead salt by a hot solution containing 40 g. of lead acetate in 200 cc. of water. The lead salt was suspended in 600 cc. of hot water, and lead sulfide was precipitated by a current of hydrogen sulfide. Quinaldinic acid was obtained by evaporation of the filtrate and recrystallized from water. It was in form of yellowish needles, melting at 156-157°. The yield amounted to 43-46% of the theoretical value.

b. Method of Hammick¹.--Quinaldine (28 g.) was brominated with 3 mole equivalents of bromine (96 g.) in a mixture of anhydrous sodium acetate (100 g.) and acetic acid (200 g.). The ω -tribromquinaldine was precipitated by pouring the reaction mixture into cold water. Recrystallized from acetic acid, it precipitated out as white thin plates, m. p. 128°. The crude product, melting at 125-127°, was directly subjected to hydrolysis by refluxing with 650 cc. of dilute sulfuric acid (1:10) for 8 hours. The solution was filtered and neutralized. Quinaldinic acid was precipitated as the copper salt by adding a solution of copper sulfate (60 g.) in 200 cc. of boiling water. The copper salt was collected on a filter and then suspended in 600 cc. of boiling water. Hydrogen sulfide was passed through the boiling solution for one hour. The quinaldinic acid was obtained by evaporation of the filtrate and recrystallized from water. The yield was 46-48% of theory, slightly higher than that obtained by the first method.

Preparation of quinaldinic acid amide, $\text{NC}_9\text{H}_6\text{.CONH}_2$ (2).--

a. Through the acid chloride.--The procedure described above (p. 9) for preparation of cinchoninic acid amide was followed. The crude product melted at 127-128°, higher than the melting point reported by Meyer² (123°). Recrystallized from acetone, the correct melting point of quinaldinic acid amide (132-133°) was reached but considerable amount of the product was lost during the recrystallization. The yield was 40% of theory.

b. Through the methyl ester.--Methyl quinaldinate was prepared by the method of Mills and Hamer³ with slight modification. Quinaldinic acid (10 g.), methanol (100 cc.) and concen-

¹Hammick, J. Chem. Soc., 123, 2882 (1923).

²Meyer, Monatsh., 25, 1199 (1904).

³Mills and Hamer, J. Chem. Soc., 121, 2011 (1922).

trated sulfuric acid (40 cc.) were refluxed for two hours. The reaction mixture was poured to 250 g. of ice water and neutralized with sodium carbonate, whereupon the ester separated out as feathery precipitate. It was collected on a filter and recrystallized from 50% methanol. It was in form of white needles, melting at 86-87°. The yield of the methyl ester was 70-79% of theory. The methyl ester (5 g.) was dissolved in methanol (15 cc.) in a pressure bottle. The solution was chilled in an ice-salt bath. Concentrated ammonium hydroxide (20 cc.) was added, followed by passing a current of ammonia gas through the solution for 15 minutes. The pressure bottle was closed and allowed to stand for 3 days. Pure quinaldinic acid amide,¹ melting at 132-133°, was obtained as hexagonal tablets and separated by filtration of the solution. The yield was 78% of theory.

Attempted synthesis of quinaldinic acid amide n-propiodide,
 $C_3H_7I \cdot NC_9H_6 \cdot CONH_2(2)$.--Quinaldinic acid amide (3 g.) was heated with n-propyl iodide (40 cc.) in a pressure bottle at 120° to 140° for 5 to 24 hours. The amide was found to remain unchanged.

Preparation of quinaldinic acid amide methiodide,
 $CH_3I \cdot NC_9H_6 \cdot CONH_2(2)$.--Quinaldinic acid amide (3 g.) was heated with dimethyl sulfate (3 g.) in an oil bath at 110°. The homogeneous solution turned to solid in 25 minutes. After heating for 2 hours, the solid was digested with ether, separated by filtration, and dissolved in 10 cc. of boiling water. Potassium iodide (6 g.) was added. A yellow precipitate came down on cooling. It was collected on a filter and recrystallized from 95% ethanol. Quinaldinic acid amide methiodide melted at 209-210°, and crystallized in form of yellowish green monoclinic narrow plates. Analysis: N, 8.73% (calculated for $C_{11}H_{11}ON_2I$, N, 8.92%). It was insoluble in cold acetic acid and ethanol but dissolved at hot. It was soluble in carbitol, very slightly soluble in cold water, more soluble in hot water. It was insoluble in benzene, acetone, carbon tetrachloride, chloroform, ether and ligroin. The yield was 37-40% of theory.

This compound was also obtained at a yield of 45% by the action of concentrated ammonium hydroxide on methyl quinaldinate methiodide. (Cf. p.10.) The latter was formed on heating quinaldinic acid methyl ester with dimethylsulfate followed by treat-

¹Späth, Monatsh., 42, 93 (1921).

ment with potassium iodide,¹ with 65% yield. Methyl quinaldinate methiodide melted at 126-127°, and crystallized in form of rhombic tablets from water.

Quinaldinic acid amide methiodide has not been previously described in literature.

Reduction of quinaldinic acid amide methiodide by sodium hydrosulfite.--Quinaldinic acid amide methiodide (1.4 g.) was dissolved in 50 cc. of boiling water. The solution was filtered, cooled down to room temperature and mixed with a solution of sodium carbonate (4.5 g.) in 15 cc. of water. A current of nitrogen was passed through the flask over the solution. Sodium hydrosulfite (4 g.) was introduced in portions. Orange color appeared for a short time. Then the solution turned turbid, followed by separation of purplish colored amorphous precipitate which was very soluble in chloroform. After one hour, the precipitate was collected on a filter, washed with water, and dried in a vacuum desiccator. A part of the solid turned to black tar. The product weighed 0.4 g. It charred at about 75° and melted at about 105°. It dissolved readily in chloroform. The chloroform solution showed very strong reducing power. The solution was immediately coated with a silver mirror when shaken with an aqueous solution of silver nitrate. It reduced potassium ferricyanide, and decolorized methylene blue instantaneously in the cold.

The solid was boiled with 250 cc. of ether. The ether filtrate on evaporation to dryness in a vacuum desiccator yielded only a trace of solid, melting at 145°, which showed slight reducing property. The portion of solid left behind after the ether extraction melted at 153-154°, and was strongly reducing.

The original aqueous solution, after separation of the above precipitate, deposited white solid on standing overnight. It was collected on a filter, washed with water, and dried. The solid weighed 0.15 g. It turned purple and then black at about 160°, sintered gradually at 180° but did not completely melt until 225°. It was soluble in chloroform, and exhibited very strong reducing property.

Both products gave negative tests for sulfur and halogen. They were insoluble in water and in dilute sodium carbonate solution. The results of nitrogen analyses indicated that both were

¹Mills and Hamer, J. Chem. Soc., 121, 2008 (1922).

the partial reduction product, N-methyl-dihydro-quinaldinic acid amide, $C_9H_7N(CH_3).CONH_2$, but impure.

Calculated for $C_{11}H_{12}ON_2$: N, 14.89%,

Found, solid m. p. 153-154°: N, 14.07%,

solid m. p. 225°: N, 13.51%.

SUMMARY

1. N-n-propyl-o-dihydro-nicotinic acid amide was prepared by the action of sodium hydrosulfite on nicotinic acid amide n-propionide in sodium carbonate solution and its properties studied.

2. Cinchoninic acid amide methiodide was reduced by sodium hydrosulfite, but isolation of the reduction product was not successful.

3. Partial reduction of quinaldinic acid amide methiodide, a new compound, by means of sodium hydrosulfite in sodium carbonate solution yielded two solids differing widely in melting points. Both were strongly reducing and their nitrogen contents indicative of the expected product, N-methyl-dihydro-quinaldinic acid amide. Both of these materials showed considerable oxytocic activity.

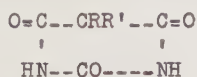
ACKNOWLEDGMENT

The writer wishes to express his appreciation to Dr. M. S. Kharasch, under whose direction this problem was done; and to Dr. M. M. Gladstone for his helpful suggestions.

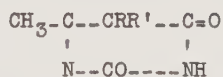
II. STUDIES TOWARD THE SYNTHESIS OF

4-METHYL-5,5-DIALKYLURACIL

Since the epoch-making synthesis of veronal from ethyl diethylmalonate and urea by Emil Fischer¹ in 1904, the barbiturates have become the most important class of hypnotics. While veronal (barbital, U. S. P.) itself has been displaced by other more therapeutically desirable compounds, a survey of the hypnotics in use reveals that they are mostly 5,5-disubstituted derivatives of barbituric acid. It is known that barbiturates in large quantities are somewhat toxic and produce undesirable after effects. Under the direction of Dr. Julius Stieglitz, the effort was made to synthesize 4-methyl-5,5-dialkyluracils. It was thought that these compounds, since they are structurally similar to barbiturates, might have hypnotic properties.



5,5-Dialkylbarbituric acid



4-Methyl-5,5-dialkyluracil

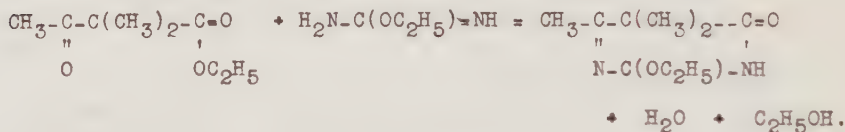
It was further assumed, since the mother substance, acetoacetic ester, is sometimes produced in the body, that its derivatives if they have hypnotic power would be less toxic than those of the barbituric acid series. In an extensive study of the uracil derivatives, Stieglitz and his students have prepared a number of 4,5-disubstituted uracils but every attempt to introduce a second group into the 5- position was unsuccessful.² At the suggestion of Dr. Stieglitz, the present investigation was undertaken. In this work the attempt was made to use the α , α -dialkyl derivative of acetoacetic ester as the starting material for condensation leading eventually to 4-methyl-5,5-dialkyluracil as the final product. Three lines of approach were studied, and these are discussed below under the appropriate headings.

¹Fischer and Diltney, Ann., 335, 334 (1904).

²Cf. Doctor's Dissertations of W. M. Bruce (1904), Basterfield (1920), E. R. Bartholomew (1933), E. R. Tweedie (1935), J. L. Southard (1936), R.E. Lidov (1936), W. P. Metzner (1937), University of Chicago.

Condensation of α, α -Dialkyl-acetoacetic Ester with Urea and Substituted Ureas

The first part of the present investigation dealt with the study of the possible reaction between α , α -dialkylacetoacetic ester and urea or the analogue of urea, under various conditions generally employed for condensation reactions. Ethyl α , α -dimethylacetoacetate was treated with urea in presence of sodium ethoxide; and with ethyl isourea at room temperature and at elevated temperatures. Ethyl α , α -diethylacetoacetate was treated with urea (a) at high temperature without a solvent, (b) in a solution of glacial acetic acid, and (c) in alcoholic solution. The same ester was treated with thiourea directly and in presence of sodium ethoxide, and with ethyl isothiurea in potassium hydroxide and in sodium ethoxide solutions. In no case were we able to isolate the desired condensation product, as, for example, 2-ethoxy-4-methyl-5,5-dimethyluracil from ethyl α , α -dimethylacetoacetate and ethyl isourea which might be expected to react according to the following scheme:



In most cases, however, the dialkylacetoacetic ester remained intact after the experiment and could be recovered quantitatively. These experiments indicate the great difference in reactivity between dialkylacetoacetic ester and dialkyl malonic ester. They also serve to illustrate the contrast between dialkylacetoacetic ester and mono-alkylacetoacetic ester. It is a well known fact that dialkylmalonic ester condenses very easily with urea in presence of sodium ethoxide, whereas mono-alkylacetoacetic ester does not react with urea directly. The latter condenses, however, readily with isourea,¹ thiourea² and isothiurea³ to form uracil derivative.

The reason for the inertness of dialkylacetoacetic ester

¹Bruce, J. Am. Chem. Soc., 26, 419 (1904).

²Johnson and Bailey, J. Am. Chem. Soc., 35, 1007 (1913).

³Wheeler and Merriam, Am. Chem. Journal, 29, 478 (1903).

toward ureas has not been clarified. It was generally ascribed to stereochemical hindrance of the two alkyl groups. However, examples are not lacking in which the ester and the ketonic radicals of dialkylacetoacetic ester take part in the reaction. Suffice it to mention that v. Auwers and Dersch¹ have prepared the phenylhydrazone of ethyl α , α -diethylacetoacetate and closed the pyrazolone ring. The overall yield was 61 per cent. Lucas² reported that by using a solution of 0.5 N barium hydroxide, ethyl α , α -diethylacetoacetate was hydrolyzed readily to 3-ethyl-2-pentanone. The yield was 31 per cent of the theoretical. In view of these facts the steric hindrance explanation for the inertness of dialkylacetoacetic ester toward ureas does not seem to be very convincing. An alternate interpretation probably lies in the absence of tautomerism, a property responsible for the characteristic reactions of acetoacetic ester. The absence of enol group in α , α -dialkylacetoacetate is deduced by v. Auwers and Wunderling³ from spectrographic analysis. The complete replacement of the hydrogen atoms in the carbon atom of acetoacetic ester, therefore, transforms it into a compound possessing only the properties of an ordinary ester. A review of literature on the condensation reactions of urea shows that it reacts most readily with compounds containing oxymethylene group. Urea does not condense with an ordinary ester, and in very few instances is urea found to react with a ketonic group in which enolization is interfered.

Attempted Synthesis of α,α -Diethyl- acetoacetyl Chloride

The second part of the investigation consists of an attempt to convert ethyl α,α -diethylacetoacetate to α,α -diethylacetoacetyl chloride, which, if formed, would be expected to condense with urea to give a ureide. Burton⁴ and James⁵ had studied the action of phosphorous pentachloride on ethyl α,α -diethylaceto-

¹v. Auwers and Dersch, Ann., **462**, 118 (1928).

²Lucas, J. Am. Chem. Soc., **51**, 251 (1926).

³v. Auwers and Wunderling, Ber., **64**, 2749 (1931).

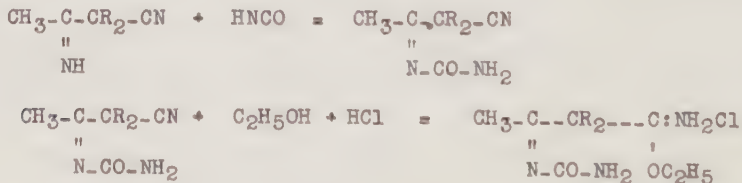
⁴Burton, Am. Chem. Journal, **4**, 395 (1882).

⁵James, Ann., **231**, 235 (1885).

acetate. They found that chlorination took place in the γ -carbon atom and that no acid chloride was produced. Since thionyl chloride has been found to be a good reagent in the preparation of acyl chlorides, it was tried on the ester in the present investigation. In a literature review on the behavior of thionyl chloride, Silberrad¹ states that this reagent as a rule can not be used with ketonic acids. Further, no reaction between an ester and thionyl chloride is mentioned in the literature. The result of this investigation showed that no acid chloride was produced by heating thionyl chloride and ethyl α,α -diethylacetoacetate. The non-formation of the acid chloride was surmised from the fact that the resulting product did not exhibit acidic properties and did not condense with ethyl isourea. Only when ethyl α,α -diethylacetoacetate was heated for a long period with a large excess of thionyl chloride was a chlorine containing product isolated. Otherwise the ester was recovered unchanged after the experiment. The study was not continued. No other attempt was made to prepare α,α -diethylacetoacetyl chloride.

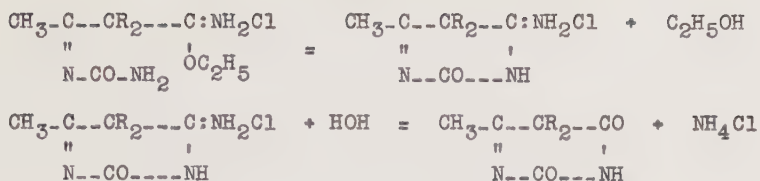
Condensation of α,α -Dialkyl- β -imino-butyronitrile
with Phenyl Isocyanate

A different line of approach toward the synthesis of 4-methyl-5,5-dialkyluracil was suggested in the condensation of isocyanic acid with α,α -dialkyl- β -imino-butyronitrile. Hübner² found that β -imino-butyronitrile condensed readily with phenyl isocyanate to form β -phenyl-ureido-butyronitrile. If the analogous reaction took place between isocyanic acid and α,α -dialkyl- β -imino-butyronitrile, we would have α,α -dialkyl- β -ureido-butyronitrile which might lead to the desired uracil according to the following scheme:



¹Silberrad, *J. Soc. Chem. Ind.*, **45**, 37, 55 (1926).

²Hübner, *J. prakt. Chem.* (2), **79**, 66 (1909).



As a preliminary investigation, α, α -diethyl- β -imino-butyronitrile was prepared and allowed to react with phenyl isocyanate. A very small amount of crystalline product was isolated which showed some indication of the presence of expected condensation product, α, α -diethyl- β -phenylureido-butyronitrile. However, the difficulty in the preparation of the starting material and the exceedingly low yield of the condensation product led to the belief that it would not be profitable to pursue the research in this direction.

EXPERIMENTAL PART

I. Reaction between Ethyl α,α -Diethylacetoacetate and Urea, Thiourea, and Isothiourea

Preparation of ethyl α,α -diethylacetoacetate,

$\text{CH}_3\text{CO.C}(\text{C}_2\text{H}_5)_2\text{COOC}_2\text{H}_5$.--This compound was prepared from ethyl acetoacetate and ethyl iodide in presence of sodium ethoxide either directly in one step or in two steps through ethyl α -ethylacetoacetate. The former procedure was found to be preferable since it involved less manipulation and gave higher yields.

a. Two-step method.--Ethyl α -ethylacetoacetate was prepared from ethyl acetoacetate and ethyl iodide in presence of sodium ethoxide according to the standard procedure.¹ Yield, 67% of theory. This ester was further ethylated to ethyl α,α -diethylacetoacetate by the method of Conrad and Limpach.² The fraction between 96° to 97.5° at 16 mm. pressure was collected. Yield, 72% of theory.

b. One-step method.--The following procedure, adopted from that of Salkowski³ for preparation of ethyl α,α -dimethylacetoacetate, was found to be very satisfactory. Ethyl acetoacetate (30 g.) and ethyl iodide (80 g.) were mixed in a 500 cc. round-bottomed flask provided with a reflux condenser. The solution was heated to boiling, and a solution of sodium ethoxide prepared from 10 g. of sodium and 175 cc. of ethanol was introduced gradually in the course of one hour. The reaction mixture was then refluxed for 3 hours. After the removal of ethanol and unreacted ethyl iodide by distilling in an oil bath at 110 - 120° , the residual oil was decanted into a separatory funnel, and washed twice with water. The washings were returned to the flask to dissolve the sodium iodide and separate out the ester. The aqueous solution was extracted with ether. The ether extract and the separated ester were combined, and shaken twice with 20% potassium hydroxide solu-

¹Vanino, "Präparativen Chemie," Stuttgart, 1923. Vol. II, p. 158.

²Conrad and Limpach, Ann., **192**, 155 (1878).

³Salkowski, J. prakt. Chemie (2), **106**, 255 (1923).

tion to remove any unchanged ethyl acetoacetate and ethyl α -ethylacetoacetate. The ether solution was dried over sodium sulfate. After distilling off the ether, the ester was rectified under reduced pressure. Practically all came over at 104-106° (20 mm. pressure). Yield, 68-70% of theory.

Reaction between ethyl α,α -diethylacetoacetate and urea without a solvent.--Ethyl α,α -diethylacetoacetate (5 g.) and urea (1.6 g.) were mixed in a test tube and heated in an oil bath at 180°. The molten urea was not miscible with the ester and remained at the bottom. After heating for 2 hours, the tube was taken out from the oil bath. The lower layer solidified while the ester layer remained unchanged. No change was observed in the ester after heating for 10 hours.

Reaction between ethyl α,α -diethylacetoacetate and urea in glacial acetic acid.--Ethyl α,α -diethylacetoacetate (5 g.), urea (1.6 g.) and glacial acetic acid (5 cc.) were mixed in a flask and heated in an oil bath at 150° for 7 hours. A homogeneous solution was produced. Upon cooling, the solution was poured into water. No solid was obtained and the unchanged ester separated out as an oil.

Reaction between ethyl α,α -diethylacetoacetate and urea in ethanol.--Ethyl α,α -diethylacetoacetate (5 g.), urea (1.6 g.) and 10 cc. of absolute ethanol were mixed in a flask. Three drops of concentrated hydrochloric acid were added. The mixture was heated in an oil bath at 150° for 12 hours. Upon cooling, urea separated out. Addition of water dissolved the urea and separated the unchanged ester.

Reaction between ethyl α,α -diethylacetoacetate and thiourea without a solvent.--Ethyl α,α -diethylacetoacetate (5 g.) and thiourea (2 g.) were heated in an oil bath at 180° for 8 hours. The two layers were not miscible. The ester remained unchanged after the experiment.

Reaction between ethyl α,α -diethylacetoacetate and thiourea in presence of sodium ethoxide.--To a solution of sodium ethoxide made from 1.5 g. of sodium and 30 cc. of absolute ethanol was introduced 5 g. of ethyl α,α -diethylacetoacetate and 2.1 g. of thiourea. The solution was heated in an oil bath at 120° for 3 hours. After removal of alcohol, the residue was taken up with water and acidified with acetic acid. White solid was obtained, weighing about 0.5 g. It was soluble in alcohol, insoluble in

ether and cold water. Recrystallized from hot water, it melted at 210-211°. Dissolving in hot sodium carbonate solution and reprecipitating by hydrochloric acid did not change the melting point. Qualitative test showed the presence of sulphur. Analysis gave N, 23.46%, C, 49.38%, H, 7.75%. The high nitrogen content excludes the possibility of being the desired condensation product, $\text{HN.CS.N:C(CH}_3\text{).C(C}_2\text{H}_5\text{)}_2\text{CO}$, ($\text{C}_9\text{H}_{14}\text{ON}_2\text{S}$, N, 14.14%, C, 54.49%, H, 7.12%). The solid was not identified.

Reaction between ethyl α,α -diethylacetoacetate and ethyl isothiourrea in presence of sodium ethoxide.--Ethyl α,α -diethylacetoacetate (5 g.) and ethyl isothiourrea hydrobromide (5 g.), prepared by the method of Wheeler and Merriam,¹ were introduced to a solution of sodium (0.65 g.) in ethanol (15 cc.). After refluxing for 3 hours, the alcohol was removed by distillation. The residue on treatment with water and acidification gave 5 cc. of oil and no solid, indicating that no condensation had taken place.

Reaction between ethyl α,α -diethylacetoacetate and ethyl isothiourrea in alkali solution.--To a solution containing 1.5 g. of potassium hydroxide in 10 cc. water was added 5 g. of ethyl α,α -diethylacetoacetate and 5 g. of ethyl isothiourrea hydrobromide. The liquid separated into two layers. Addition of alcohol (10 cc.) did not result in a homogeneous solution. After vigorous shaking and long standing, no solid separated out and no change was observed in the two layers.

II. Action of Ethyl α,α -Dimethylacetoacetate on Urea and Isourea

Reaction between ethyl α,α -dimethylacetoacetate and urea in presence of sodium ethoxide.--This experiment was used as a critical test whether α,α -dialkylacetoacetic ester reacted similarly to dialkylmalonic ester. Fischer's procedure² for the formation of veronal was repeated as a parallel test, and the following observation was noted.

Diethylmalonic ethyl ester (10 g.) and pulverized urea (4 g.) were introduced to a pressure bottle containing 3.2 g. of sodium dissolved in 60 g. of absolute ethanol. The pressure bottle

¹Wheeler and Merriam, Am. Chem. Journal, 29, 478 (1903).

²Fischer and Dilthey, Ann., 335, 334 (1904).

was put in an oil bath at 108° . The reaction mixture quickly formed a clear solution and then turned turbid followed by precipitation of crystalline solid. After heating for five hours, the solution was cooled and the solid collected on filter. It was the sodium salt of veronal, weighing 9 g. after air dried. The salt was dissolved in 35 cc. of water and acidified with hydrochloric acid. White crystalline precipitate was obtained and separated from the solution by filtration. After drying at 105° , it weighed 6.5 g. (78% of theoretical yield) and melted at $185-187^{\circ}$. Recrystallization once from water gave it the correct melting point of pure veronal, $190-191^{\circ}$.

The above procedure was followed closely using an equivalent quantity of ethyl α,α -dimethylacetoacetate in place of diethylmalonic ester. No precipitate separated out from the reaction mixture. Upon treatment with hydrochloric acid, no solid product was obtained.

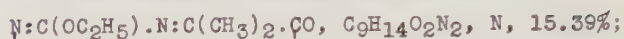
In a second experiment, the mixture of ethyl α,α -dimethylacetoacetate and urea in sodium ethoxide solution was heated at $125-130^{\circ}$. Some amorphous precipitate separated out. More solid came down upon cooling. When the stopper was opened, strong odor of ammonia was noticed. The solid was separated by filtration of the solution. It was dissolved in water and acidified with hydrochloric acid. Effervescence took place and no solid precipitate was produced. The gas evolved was found to be carbon dioxide.

Reaction between ethyl α,α -dimethylacetoacetate and ethyl isourea.--Ten g. of ethyl α,α -dimethylacetoacetate and 7 g. of ethyl isourea¹ were mixed together in a weighing bottle. The mixture was divided into three equal portions which were treated separately as follows:

Portion A was put in a desiccator over concentrated sulfuric acid and potassium hydroxide beads. After three days, the liquid turned viscous. The desiccator was now evacuated. A week later, the pasty mass was agitated with ether. White solid separated out and was collected on a filter. The filtrate upon evaporation of the solvent gave oily residue with the smell of unchanged dimethylacetoacetic ester. The solid obtained weighed 1.2 g. Recrystallized from alcohol, it formed microscopic tablets and melted at 295° with effervescence. Analysis gave N, 31.62%.

¹W. L. Terre, Master's thesis, University of Chicago, 1932.

Calculated for the desired condensation product,



The solid was boiled with hydrochloric acid and the solution filtered. White precipitate came down upon cooling. It did not melt at 310° . Analysis: N, 32.98%.

Portion B was heated in an oil bath at 50° for 5 minutes and then placed in the desiccator. After three days, the mixture turned to a gummy paste. By agitation with ether, white solid was isolated. It was boiled with dilute hydrochloric acid and the precipitate obtained upon cooling was recrystallized from water. The product gave strong Beilstein's test for halogen and did not melt at 300° . Analysis: N, 32.63%.

Portion C was heated in an oil bath at $50-60^\circ$ for 30 minutes. No change was observed. When the temperature of the oil bath was raised to 63° , gas was liberated and white precipitate appeared. The mixture was heated at $63-65^\circ$ for 30 more minutes before transferring into the desiccator. After three days, the solid was separated from the gummy mass by means of ether. It was boiled with dilute hydrochloric acid and the precipitate obtained upon cooling was recrystallized from 70% ethanol. The product did not melt at 320° . It gave strong halogen test. Analysis: N, 43.90%. The ether solution upon evaporation gave oily residue with the smell of the original ethyl α,α -dimethylacetoacetate.

The high nitrogen contents of the products and the fact that considerable amount of unchanged dimethylacetoacetic ester was recovered indicated that the desired condensation between ethyl α,α -dimethylacetoacetate and ethylisourea had not taken place. The solids obtained were not identified.

III. Reaction between Ethyl α,α -Diethylacetoacetate and Thionyl Chloride

Reaction in benzene solution.--Ethyl α,α -diethylacetoacetate (5 g.), thionyl chloride (3.2 g.) and dry benzene (10 cc.) were refluxed for 2 hours. After removal of the low boiling constituents, the residue was distilled under reduced pressure. It came over at $117-118^\circ$ at 28 mm. pressure, and weighed 5 g. The distillate showed no reaction with sodium hydroxide or silver ni-

trate solutions.

Reaction under pressure.--Ethyl α,α -diethylacetoacetate (5 cc.) and thionyl chloride (6 cc.) were mixed in a sealed tube and heated for one hour at 100° in one experiment and at 170° in another. The ester was recovered unchanged in both cases.

Reaction in large excess of thionyl chloride.--Ethyl α,α -diethylacetoacetate (5 g.) and thionyl chloride (15 cc.) were refluxed for 20 hours. After removal of thionyl chloride, the liquid was distilled under reduced pressure. Two cc. of high boiling fraction was obtained. It contained 10.35% Cl (calculated for $\text{CH}_3\text{CO.C}(\text{C}_2\text{H}_5)_2\text{COCl}$, $\text{C}_8\text{H}_{13}\text{O}_2\text{Cl}$, Cl, 20.07%). The product did not show reactions of acid chloride. When treated with ethyl isourea, the mixture turned to gummy mass. The gum when boiled with dilute hydrochloric acid separated some yellow solid upon cooling. Analysis gave N, 33.17%. The product was not identified. It is interesting to note, however, that in the reaction between ethyl α,α -dimethylacetoacetate and ethyl isourea, solids of about the same nitrogen content were produced.

IV. Reaction between α,α -Diethyl- β -imino-butyronitrile and Phenyl Isocyanate

Preparation of α -ethyl- β -imino-butyronitrile,

$\text{CH}_3\text{C}(:\text{NH}).\text{CH}(\text{C}_2\text{H}_5).\text{CN}$.--The method of Warnecke¹ was followed. Acetonitrile (100 g.) was introduced slowly into a three-necked flask containing 37.5 g. of sodium covered with 350 cc. of dry benzene, the flask being heated in an oil bath at 85° . The mixture was kept in the oil bath for 7 hours. The sodium salt of β -imino-butyronitrile was gradually formed. On the next day, the sodium salt was separated from the solution by filtration and washed with dry benzene. It was then transferred to a 1-liter round bottomed flask and a solution of ethyl bromide (190 g.) in dry benzene (95 cc.) was added. The mixture was heated in an oil bath at $73\text{--}75^\circ$ for 7 hours. The supernatant liquid was separated by decantation. The solid residue was dissolved by addition of water (250 cc.), and the benzene solution was again separated. The aqueous layer was extracted three times with 50 cc. portions of benzene. The separated benzene solutions were combined and

¹Georg Warnecke, Doctor's Dissertation, p. 15, Heidelberg, 1903.

dried over sodium sulfate. After distilling off the benzene with a water pump, the liquid was rectified at 5 mm. pressure with an oil pump. The portion coming over at 120-135° was collected and redistilled. The product acquired a light yellow color. The yield was 70 g. (58% of theory).

Preparation of α,α -diethyl- β -imino-butyronitrile,
 $\text{CH}_3.\text{C}(:\text{NH}).\text{C}(\text{C}_2\text{H}_5)_2.\text{CN}$.--For the introduction of the second ethyl group to the α - carbon atom, the following method, developed by Dr. E. W. Lowe,¹ was employed. Sodium (7.3 g.) was made in form of globules by melting it in boiling xylene and shaking the flask during cooling to break up the metal. The sodium was introduced to a three-necked flask containing 200 cc. of dry benzene. The flask was heated in an oil bath at 90°. α -Ethyl- β -imino-butyronitrile (35 g.) was introduced in the course of one and one-half hours. The reaction mixture was refluxed for 4 hours longer and allowed to stand overnight. Ethyl iodide (50 g.) was added and the solution again refluxed for 6 hours. Upon cooling, the liquid was filtered off. The solid was returned to the flask, covered with 100 cc. of benzene and chilled in ice-salt bath. A saturated solution of ammonium chloride in ice water was added and the mixture rapidly agitated. The benzene layer which at first solidified was allowed to melt and separated rapidly. The aqueous layer was again extracted with 50 cc. of benzene. The benzene solutions were combined and dried over sodium sulfate. After removal of benzene, the oil was distilled at 2-1 mm. pressure. About 15 cc. came over below 120°. The second fraction, containing mainly the diethyl compound, was collected between 120° to 125°. This was again rectified. The main portion, boiling at 118-120° at 1 mm. pressure, was used for the following experiments. The yield was 15 g. (34% of theory).

Reaction between α,α -diethyl- β -imino-butyronitrile and phenyl isocyanate at high temperature.-- α,α -Diethyl- β -imino-butyronitrile (2.7 g.) and phenyl isocyanate (2.4 g.) were put in a sealed tube and heated in an oil bath at 150° for 5 hours. The gummy solid was dissolved in a small volume of chloroform. Low boiling ligroin was added whereupon some semi-solid precipitated out. The solvent was decanted. The semi-solid residue was treated with ethanol and the solution filtered. On standing, the

¹E. W. Lowe, Unpublished work.

ethanol solution precipitated a yellowish crystalline substance which sintered at about 145° and completely melted at about 190° . It was purified by recrystallization from ethanol. A part dissolved in hot ethanol readily and melted at $140-143^{\circ}$. The remaining portion was recrystallized by using a large volume of ethanol and the product melted at $229-231^{\circ}$. The yields were very small.

Reaction between α,α -diethyl- β -imino-butyronitrile and phenyl isocyanate at room temperature.-- α,α -Diethyl- β -imino-butyronitrile (2.7 g.) and phenyl isocyanate (2.4 g.) were mixed in a sealed tube and allowed to stand at room temperature. The mixture gradually became very viscous. Some crystals were observed in 40 days. The tube was opened after 60 days. The solid was separated from the viscous liquid by repeatedly washing with benzene. The solid thus obtained melted at $139-140^{\circ}$. It weighed about 0.2 g. Recrystallized from ethanol, it was obtained in form of fine white monoclinic plates, melting at $144-145^{\circ}$. When mixed with phenyl urea (m. p. 145°), the melting point lowered to $133-136^{\circ}$. The compound was then identified by analysis to be α -ethyl- β -phenylureido-butyronitrile, $\text{CH}_3\text{.C}(\text{:N.CO.NHC}_6\text{H}_5)\text{.CH}(\text{C}_2\text{H}_5)\text{.CN}$, a condensation product between α -ethyl- β -imino-butyronitrile and phenyl isocyanate.

Calculated for $\text{C}_{13}\text{H}_{15}\text{ON}_3$: C, 68.10%; H, 6.60%; N, 18.34%.

Found : C, 68.13%; H, 6.47%; N, 18.53%, 18.49%.

This compound was probably produced by the α -ethyl- β -imino-butyronitrile which had not been completely removed from the α,α -diethyl- β -imino-butyronitrile in the process of fractional distillation. It was insoluble in water, ligroin and carbon tetrachloride; soluble in ether, acetone, carbitol, chloroform, and glacial acetic acid. It dissolved slightly in cold ethanol, and very readily in hot ethanol. α -Ethyl- β -phenylureido-butyronitrile was not known in literature.

The benzene solution of the gum after the separation of the above solid was evaporated in a vacuum desiccator. The residue was dissolved in hot ethanol and the solution was then chilled in the ice-salt bath. Fine crystals separated out. They were collected on a filter and recrystallized from ethanol and from benzene. The solid was in form of white needles, melting at $233-234^{\circ}$. The results of analysis seemed to indicate that it was the impure α,α -diethyl- β -phenylureido-butyronitrile, $\text{CH}_3\text{.C}(\text{:N.CO.NHC}_6\text{H}_5)\text{.C}(\text{C}_2\text{H}_5)_2\text{.CN}$, the expected condensation product

between α,α -diethyl- β -imino-butyronitrile and phenyl isocyanate.
Calculated for $C_{15}H_{19}ON_3$: C, 70.00%; H, 7.45%; N, 16.33%,

Found : C, 68.73%; H, 6.91%; N, 15.54%, 15.47%.

The product was not further studied due to lack of material.

SUMMARY

1. The following reactions were studied with the object to synthesize 4-methyl-5,5-dialkyluracils.

2. It was found that α,α -dialkylacetoacetic esters did not condense with urea, isourea, thiourea and isothiurea to give ureide or pyrimidine derivatives.

3. Attempt to prepare α,α -diethylacetoacetyl chloride by the action of thionyl chloride on ethyl α,α -diethylacetoacetate resulted in some chlorination product but not the expected acid chloride.

4. Indication was found that α,α -diethyl- β -imino-butyronitrile condensed with phenyl isocyanate to form α,α -diethyl- β -phenylureido-butyronitrile, but the yield was very small. α -Ethyl- β -phenylureido-butyronitrile, previously unknown, was identified as a by-product.

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